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In This Issue

Fenofibrate (Tricor®): A Brief Review

Introduction

Micronized fenofibrate is a fibric acid derivative approved by the Food and Drug Administration in February of 1998 for the treatment of hyperlipidemia. Other fibrates currently available on the U.S. market are gemfibrozil and clofibrate. In general, fibric acid agents significantly lower triglyceride levels, but few data are available comparing the three agents.[1] Fenofibrate also may have beneficial non-lipid effects such as reduction of fibrinogen and uric acid levels.[1]

Description

Micronized fenofibrate (Tricor®) is available as 67-mg, 134-mg, and 200-mg hard gelatin capsules for oral administration. Each capsule also contains lactose, pre-gelatinized starch, sodium lauryl sulfate, crospovidone, and magnesium stearate.[2] Tricor® is manufactured by Abbott Laboratories.

Indication

Tricor® is indicated as an adjunct to diet for the treatment of adults with hypertriglyceridemia (types IV and V hyperlipidemia) who have not responded adequately to diet therapy and who are at risk for pancreatitis.[2] Recently the labeling indication for Tricor® was expanded to include mixed hyperlipidemia (type II hyperlipidemia).[2]

Pharmacology

Fenofibrate is rapidly hydrolyzed after oral ingestion to its pharmacologically active form, fenofibric acid.[2] Fenofibrate, like other fibrates, limits the availability of fatty acids for triglyceride synthesis within the liver, increases lipoprotein lipase activity, stimulates reverse cholesterol transport, and suppresses activity of HMG-CoA reductase within the liver.[3] The lipid modifying effects include a substantial reduction in plasma triglycerides, a reduction in LDL and total cholesterol, and an increase in HDL cholesterol.[4] Fenofibrate enhances VLDL catabolism by stimulating lipoprotein lipase and reduces hepatic synthesis and secretion of VLDL.[1] On a molecular level, fenofibrate activates peroxisome proliferator activated receptors (PPARs) which are nuclear hormone receptors that control a number of genes involved in lipid metabolism, including the genes encoding apolipoprotein C-III production.[1,5] Apolipoprotein C-III synthesis in the liver is reduced and plasma concentrations are decreased.[1,6] Since apolipoprotein CIII inhibits lipoprotein lipase activity, the net effect is increased clearance of chylomicrons and VLDL.[1,6] HDL levels are increased due to the reduction in VLDL levels which results in decreased transfer of cholesteryl ester from HDL to VLDL.[5] Apolipoprotein AI (ApoI) and apoliprotein AII (Apo II) are major protein constituents of HDL.[4] Levels of ApoI and ApoII are increased by fenofibrate and promote reverse cholesterol transport.[2,4] PPAR transcription of APOI and APOII genes may play a role in the increase in HDL cholesterol.[4] The reduction in triglyceride levels also causes a shift in the LDL profile to a larger, lighter, more buoyant particle which is less atherogenic and more likely to be taken up by the LDL receptor.[4,5]

Pharmacokinetic

The absolute bioavailability of fenofibrate cannot be determined due to its insolubility in aqueous media for injection.[2] The micronized form of fenofibrate has enhanced absorption over the non-micronized formulation. A 67-mg micronized fenofibrate capsule produces similar plasma concentrations of fenofibric acid as three, 100-mg non-micronized fenofibrate capsules.[7] The micronized formulation results in less variability in the maximum concentration, minimum concentration, and area under the

plasma-concentration-time curve.[7] After oral administration, peak plasma levels of fenofibric acid occur within 6 to 8 hours.[2] Absorption of micronized fenofibrate is increased by approximately 35% when administered with food.[2] Steady-state plasma levels in healthy volunteers were reached within 5 days of dosing with single oral doses of 67 mg.[2] After multiple daily doses, accumulation of fenofibric acid did not occur.[2] Fenofibrate is highly protein bound (approximately 99%) in both healthy and hyperlipidemic patients.[2] It is rapidly and completely hydrolyzed by esterases to an active metabolite, fenofibric acid.[2] The metabolite is primarily conjugated with glucuronic acid and excreted in the urine.[2] The half-life of fenofibrate is approximately 20 hours.[2,7]

Selected Clinical Trials

The effect of fenofibrate on serum triglycerides was evaluated in a randomized, double-blind, placebo-controlled clinical trial of 147 patients with Type IV and V hypertriglyceridemia.[8] Patients were assigned to treatment groups according to their mean fasting triglyceride level: group 1 had triglyceride levels from 350 mg/dl to 499 mg/dl (n=55) and group 2 had levels from 500mg/dl to 1500mg/dl (n=92).[8] Patients within each group were randomized to receive fenofibrate (non-micronized) 100 mg three times a day or placebo. Mean percent changes from baseline to end of therapy for fenofibrate group 1 were a 46%, 44%, and 9% decrease in triglycerides, VLDL-triglycerides (VLDL-TG), and total cholesterol, respectively.[8] HDL increased by a mean of 20%.[8] In group 2 the mean percent decrease in triglycerides, VLDL-TG, and total cholesterol was 55%, 51%, and 9%, respectively.[8] The mean percent increase in HDL was 23%, and LDL increased by a mean of 45%.[8] The differences in the primary outcome measures in both treatment groups reached statistical significance when compared to placebo. The change in triglycerides and VLDL-TG was more pronounced in patients with very high baseline triglycerides, but this same group experienced an increase in LDL. The effects of fenofibrate on LDL levels has been reported to be variable depending on the type of hyperlipidemia.[1] In patients with hypertriglyceridemia, LDL particles are small and more dense, and the low levels of LDL have been attributed to an increase in catabolism by the non-receptor pathway.[9] Treatment with fenofibrate in this condition slows down the rate of LDL clearance and switches the catabolism to the receptor pathway which leads to the production of a larger, lighter, and less atherogenic LDL particle.[9]

The effects of fenofibrate at a dose equivalent to 200 mg of Tricor® per day were assessed in double-blinded clinical trials in patients with hypercholesterolemia and mixed dyslipidemia (types IIa and IIb).[2] Total cholesterol decreased by 17% to 22%, LDL decreased by 20% to 31%, triglycerides decreased by 24% to 36%, and HDL increased by 10% to 15%.[2] Various open-label studies of fenofibrate in Types IIa and IIb hyperlipidemia have reported similar effects.[1]

Very little information is available comparing fenofibrate to gemfibrozil. In a small (n=12) single-blinded, randomized, crossover study in Chinese patients with Type IIb hyperlipoproteinemia, effects on triglycerides were similar in patients treated with fenofibrate and gemfibrozil.[10] The fenofibrate treatment group had a greater reduction in LDL and total cholesterol compared to the gemfibrozil group.[10] Larger studies comparing both drugs are needed.

Comparative trials of micronized fenofibrate and the HMG-CoA reductase inhibitors simvastatin (20 mg) and pravastatin (20 mg) in patients with hypercholesterolemia and hypertriglyceridemia revealed a much greater decrease in triglycerides (30% to 50%) in the fenofibrate group as well as a slightly greater increase in HDL cholesterol levels (1% to 34%).[4] In general, fenofibrate was less effective than either simvastatin or pravastatin in lowering LDL cholesterol (17% versus 33%).[4] In an open-label, randomized study of atorvastatin 10 mg or 20 mg per day compared to fenofibrate 100 mg three times a day, atorvastatin was less effective in lowering triglyceride levels or raising HDL.[11] As demonstrated in comparisons with other HMG CoA reductase inhibitors, fenofibrate was less effective in reducing LDL and total cholesterol than atorvastatin.[11]

Fenofibrate has a beneficial effect on fibrinogen and uric acid levels.[4,12,13,14] Elevated plasma fibrinogen may be an independent risk factor for cardiovascular disease.[15] Fenofibrate has been shown to decrease plasma fibrinogen levels by 15% and decrease uric acid levels by 13%.[12] Fibrinogen levels in patients with dyslipidemia have generally decreased from about 7% to 23%.[4] The fibrinogen-lowering effect of fenofibrate has been shown to be greater than that of simvastatin or pravastatin.[4] In one study, after 4 months of treatment, fenofibrate decreased fibrinogen levels by 16%, whereas gemfibrozil increased levels by 20%, and no changes occurred with simvastatin or pravastatin.[13] Significant decreases in uric acid levels have also been documented in other clinical trials.[4,14] Although still controversial, elevated uric acid levels have been proposed as a risk factor for coronary heart disease.[16] The uricosuric effect of fenofibrate may also be an added benefit in patients with gout.

Adverse Effects

Most of the adverse event data for fenofibrate is derived from European studies using the non-micronized formulation which has been available in Europe since 1975.[17] Overall the most frequently reported adverse event, causing discontinuation of fenofibrate in 1.6% of patients, was an increase in liver function tests.[2] In European trials the most common adverse events (occurring in 6% of patients) were gastrointestinal symptoms, muscle pain, skin problems, sweating, and dizziness.[17] Postmarketing spontaneous reporting of adverse events included liver enzyme changes, hepatitis, gallstones, cutaneous skin reactions, photosensitivity, eosinophilia, leukopenia, asthenia, and weight loss.[17] In general, the rate of reactions has been low, with an annual incidence rate of 0.3%.[17] The U.S. trials revealed similar adverse effects with skin reactions, neurologic reactions, and musculoskeletal reactions occurring more often in the fenofibrate groups than the placebo groups.[17]

In a 12-week drug monitoring program with micronized fenofibrate, adverse events were reported in 3.8% of the 9884 patients studied.[18] The most frequently reported adverse events were similar to the events reported with the non-micronized formulation.[18] Only one case of hepatitis and two cases of cholelithiasis were reported.[18]

Drug Interactions

Fenofibrate has been reported to potentiate the anticoagulant effect of warfarin.[19] This can occur within 5-10 days after initiating fenofibrate in patients receiving long-term warfarin therapy.[19] Three-times-a-week PT/INR monitoring, and dose reduction of warfarin to maintain PT/INR in the desired range, have been suggested when fenofibrate is initiated.[2,19]

Since bile acid sequestrants are known to bind other drugs, the manufacturer recommends spacing fenofibrate either one hour before or 4 to 6 hours after cholestyramine and colestipol.[2] Fenofibrate may increase the nephrotoxicity of cyclosporine.[5] Rises in serum creatinine have been reported.[1] The manufacturer suggests using the lowest effective dose of fenofibrate in patients taking cyclosporine or other nephrotoxic agents.[2]

Due to a potential increase in the risk of rhabdomyolysis, the manufacturer cautions against the use of fenofibrate with HMG CoA reductase inhibitors unless the benefits outweigh the risks.[2] In a long-term efficacy and safety trial of fenofibrate 200 mg with either pravastatin 20 mg or simvastatin 10 mg, 10% of patients had transient elevations of serum alanine aminotransferase (ALT) greater than 2 times the upper limit of normal.[14] Only 2.5% had an isolated and transient increase of creatine kinase without muscle symptoms.[14] Neither of these results were statistically significant, and none of the patients experienced myopathy.[14] The use of low-dose statins with fenofibrate appears to be well tolerated. However, it is unclear if higher doses or use of this combination in patients with renal or hepatic insufficiency could increase the risk.[2]

Precautions and Contraindications

Tricor® is contraindicated in patients with hypersensitivity to fenofibrate, severe renal disease, or preexisting gallbladder disease.[2] Tricor® is also contraindicated in patients with hepatic dysfunction, including biliary cirrhosis.[2]

Precautions include risk of pancreatitis and myopathy.[2] Transient hematologic changes have been reported. Thrombocytopenia and agranulocytosis have been reported rarely.[2] Tricor® is not recommended in nursing mothers, and the safety and efficacy of the drug has not been established in pediatric patients.[2] The fenofibrate dose should be reduced in the presence renal insufficiency.[2]

Dosage and Administration

The dose of fenofibrate for primary hypercholesterolemia or mixed hyperlipidemia is 200 mg daily. For hypertriglyceridemia, the dose is 67 mg to 200 mg daily. The maximum daily dose of fenofibrate is 200 mg. Doses of 67 mg daily are recommended in patients with impaired renal function and the elderly. Lipid levels should be monitored periodically, and the dosage decreased if levels fall significantly below target range.[2]

Cost

Drug	Dose	Cost Per Month*
Gemfibrozil	600 mg twice daily	$ 3.53
Tricor®	67 mg once daily	$12.30
Tricor®	134 mg once daily	$26.00
Tricor®	3 X 67 mg once daily	$36.90
Tricor®	200 mg once daily	$40.60

* Federal Supply Schedule

Conclusions

Fenofibrate appears to lower triglyceride and LDL levels and increase HDL levels. It is effective in the treatment of mixed hyperlipidemia (Type II) and hypertriglyceridemia. Further study is needed to determine whether the lipid-modifying effects and the fibrinogen and uric acid lowering improve cardiovascular outcomes. Fenofibrate has been used for many years in Europe and has been well tolerated.[17] Data comparing fenofibrate to gemfibrozil are limited and inconclusive. Fenofibrate has the advantage of once daily dosing but is more expensive than gemfibrozil.

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Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Fenofibrate (Tricor), an oral antihyperlipidemic
- Atovaquone/Proguanil (Malarone), an oral antimalarial
- Lopinavir/Ritonavir (Kaletra), an oral protease inhibitor for the treatment of HIV infection

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